UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/723,316	11/28/2000	Daniel Dupret	746220-0005(58763.000004)	6162

22204 7590 01/15/2003

NIXON PEABODY, LLP
8180 GREENSBORO DRIVE
SUITE 800
MCLEAN, VA 22102

EXAMINER	
HASHEMI, SHAR S	

ART UNIT	PAPER NUMBER
1637	12

DATE MAILED: 01/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/723,316	DUPRET ET AL.	
	Examiner	Art Unit	
	Shar Hashemi	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29 and 31-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29 and 31-39* is/are rejected.

7)☒ Claim(s) *1, 4-35, 37, and 39* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 May 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Specification

1. This application should be examined for errors: At page 12, line 1, "abilityto" should be rewritten as "ability to" and at line 3 "Forexample" rewritten as "For example"; at claim 34, page 33, line 24, "librarys" should be rewritten as "libraries"; at claim 35, on page 33, line 31, "anyone" should be changed to "any one." Furthermore, the spelling of QUIAGEN system (i.e. Quiaquick , Qiaquick) is inconsistent. The specification must be amended to correct these and all other errors.

2. The use of the trademarks "AMPLIGASE" (page 16, see table II; page 19, see table IV), "Qiaquick system" (page 17, line 16; page 18, line 24), "QIAquick column" (page 19, line 2), "Wizard PCR Preps system" (page 21, line 9) has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

3. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

4. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) or
REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)
(e) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) BRIEF SUMMARY OF THE INVENTION.
(g) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(h) DETAILED DESCRIPTION OF THE INVENTION.
(i) CLAIM OR CLAIMS (commencing on a separate sheet).
(j) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(k) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Claim Objections

5. Claims 1, 4-35, 37, and 39 are objected to because of the following informalities:

A) Claim 30 is missing and therefore should be canceled or amended. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they

must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

B) Claim 19, on page 31, line 11, "11 , 13" should be changed to "11 and 13."

C) Claim 29, on page 32, line 33, "single or double-stranded oligonucleotides complementary just" should be changed to "only those single or double-stranded oligonucleotides which are..."

D) Claim 32, on page 33, line 10, "thanks to" should be changed to "by utilizing."

6. Claims 4-35 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). However, an attempt has been made to examine the merits of the claims.

7. Claim 16 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). However, an attempt has been made to examine the merits of the claims.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

A) Claims 1-29 and 31-39 are indefinite because the phrase "if it/they is/are not present..." in step (b) of claim 1 is confusing. It is unclear as to which fragments are being utilized in step

(c). Furthermore, step (c) is incomplete. The claim should be amended to incorporate which fragments are hybridized to the assembling templates in step (c).

B) Claims 1-39 are indefinite because the limitation "possibly in the presence of..." in step (b) of claim 1 is both vague and indefinite. As it does not merely present alternatives of A or B but the presence of A or B. It is suggested that the claim be reentered as two separate claims to obviate the rejection.

C) The phrase "characterized in that" renders claims 1-29 and 31-39 indefinite. It is unclear as to what "characterized in that" encompasses. The claims should be amended to delete the phrase "characterized in that" and incorporate "comprising" or "consisting of" language.

D) The phrase "and/or" renders claims 13, 14 and 16 indefinite. It is unclear as to whether the claims refer to "step (c) and step (d)" or "step (c) or step (d)." The metes and bounds of the claim is vague.

E) The phrase "generated starting from a native gene by steps of..." renders claim 17 indefinite. It is unclear as to which method is utilized to "generate" the initial library of polynucleotide. The claim should be amended to incorporate the "selected from the group consisting of..." language.

F) The phrase "RLR reaction" renders claims 21 and 23 indefinite. Even though the specification discloses the definition at page 19, line 9, it is unclear for one of ordinary skill in the art as to which method steps are utilized in the "RLR reaction." The claims must be amended to incorporate a definition of the "RLR" abbreviation.

G) Regarding claim 6, the phrase "such that" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

H) The phrase "same initial library" renders claim 22 indefinite. It is unclear as to whether "same initial library" refers to the "initial library" of claim 7 or a different "same initial library."

I) Claim 7 recites the limitation "the initial library" in page 29, line 14. There is insufficient antecedent basis for this limitation in the claim. Furthermore, it is unclear if "a library" recited in claim 1 is in fact the "the initial library" of claim 7, or that, "the initial library" of claim 7 refers to a library from which "a library" of claim 1 was made.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who

has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

10. Claims 1-13, 15, 17-29 and 31-39 are rejected under 35 U.S.C. 102(e) as being anticipated by Stemmer (US 6,117,679 September 12, 2000).

Stemmer teaches a process of obtaining *in vitro* recombined polynucleotide sequences utilizing a library of polynucleotide sequences comprising fragmenting the double-stranded polynucleotide sequences of a library, denaturing the fragments possibly in the presence of one or more assembling templates, hybridizing the fragments with one or more assembling templates if the fragments are not present in the denaturing step, ligating the fragments in order to obtain recombined polynucleotide sequences, selecting the recombined polynucleotide sequences having advantageous properties compared to the corresponding properties of one or more reference sequences (see whole document, especially col. 4, line 23 to col. 8, line 45). At the end of the ligating step and before the selecting step, he teaches repeating the denaturing, hybridizing, and ligating steps utilizing the ligated and non-ligated fragments resulting from the ligating step (col.5, lines 19-40). Before the selecting step, he teaches separating the recombined polynucleotide sequences from the assembling template or templates (col. 5, lines 19-40). Before the selecting step, he also teaches amplifying the double-stranded recombined

polynucleotide sequences (col. 5, lines 30-45). Before the selecting step, he teaches cloning the recombined polynucleotide sequences possibly after separating the recombined strands of the template or the templates (col. 5, lines 30-45). He teaches the ends of the fragments that were generated at the fragmenting step permits adjacent hybridization of these ends on the assembling template during the hybridizing step and ligation of these fragments with each other during the ligating step (col. 5, lines 30-45). He teaches the polynucleotide sequences of the initial library have zones of homology either between themselves or with the assembling templates in order to generate ends of fragments at the fragmenting step which permit adjacent hybridization of these ends on the assembling templates at the hybridizing step and ligation of these fragments with each other at the ligating step (col. 5, lines 35-46). He teaches simultaneously carrying out the hybridizing and ligating steps (col. 5, lines 20-43). He teaches carrying out the fragmenting step in a controlled or random manner (col. 5, lines 35-67) . He teaches the fragmenting step consists of subjecting the polynucleotide sequence of the initial library to a hydrolysis by the action of one or more restriction enzymes (col. 5, lines 45-67). He teaches the degree of recombination and the position of the points of recombination and the position of the points of recombination of the recombined polynucleotide sequences are determined by the fragmentation in the fragmenting step when carried out in a controlled manner (col. 5, lines 45-67). He teaches the random fragmenting of the polynucleotide sequences in the fragmenting step is carried out by any enzymatic or mechanical means (col. 31, lines 19-24). He teaches enzymes capable of recognizing and cutting non-hybridized ends of the fragments in a specific manner are added at the hybridizing step and ligating step when the ends overlap with other hybridized fragments on the same template (col. 5, lines 38-62).

Additionally, he teaches the ligase used in the ligating step is active at high temperatures and thermostable (col. 67, lines 20-43). In the production of an initial library of polynucleotide sequences, he teaches utilizing a native gene in error prone PCR (col. 8, lines 19-43). He teaches the initial library of double-stranded polynucleotide sequences is made with synthetic sequences that will be fragmented in the fragmenting step (col. 5, line 18-45). He teaches the fragmenting step consists of subjecting the initial library to a hydrolysis by the action of restriction enzymes which have a large number of cutting sites on the polynucleotide sequences of the initial library (col. 5, lines 22-50). He teaches the fragmenting step consists of a random treatment with DNAse I of an initial library of partially heterologous, double-stranded polynucleotide sequences (col. 29, lines 9-25). He teaches fragments which are generated by a random treatment are used as templates for each other, for the hybridization in the course of the hybridizing step (col. 5, lines 18-36). He teaches the denaturing step is carried out by combining at least two distinct libraries of fragments, where the distinct libraries are created after the initial library is treated with different restriction enzymes (col. 5, lines 18-30). He teaches the fragments obtained in the fragmenting step by a treatment with restriction enzymes are used as templates for each other (col. 5, lines 18-61). He teaches the fragments of the fragmenting step are obtained by amplification reactions directed by the polynucleotide sequence of the initial library (col. 5, lines 18-61). He teaches the amplification reaction is carried out with oligonucleotide primers permitting generation of fragments whose ends are adjacent along the whole length of the assembling sequence (col. 5, lines 18-49). He teaches the amplification reactions are carried out with oligonucleotide primers permitting generation of fragments having common sequences, where the fragments serve as the assembling template for each other at the denaturing step (col.

5, lines 18-49). He teaches the initial library is fragmented into *n* fragments, where *n* is three or more (col. 11 line 14 to col. 12, line 65). He teaches the assembling template in the denaturing step is a polynucleotide sequence resulting form the initial library (col. 5, lines 18-62). He teaches only those single-stranded oligonucleotides which are complementary at the 3' end of one fragment and at the 5' end of the adjacent fragment are used as assembling template in the denaturing and hybridizing steps (col. 4, line 38 to col. 5, line 40). He teaches template and single-stranded oligonucleotides of variable length are added in the denaturing step (col. 6, line 53 to col. 7 line 4). Before the selecting step, he teaches a label present on the assembling template assists in the separation of the recombined polynucleotide sequences from the assembling template (col. 8, lines 20-44). He teaches the recombined polynucleotide sequences obtained in the ligating step and possibly cloned are screened by any appropriate means in order to select the recombined polynucleotide sequences (col. 5, line 40 to col. 6, line 15). He teaches the initial library of polynucleotide sequences is formed by at least one library, where the library is prepared by the previously described process and possibly mixed with other polynucleotide sequences (col. 5, line 18 to col. 6, line 15).

He teaches a vector containing a recombined polynucleotide sequence having one or several advantageous properties as compared to the corresponding properties of reference sequences obtained and selected by the previously described process (col. 6, lines 10-15; col. 29, line 56 to col. 30, line 15). He teaches a cellular host cell transformed by the recombined polynucleotide sequence (col. 29, line 40 to col. 30, line 46). He teaches a protein encoded by the recombined polynucleotide sequence (col. 14, line 65 to col. 15, line 20). He teaches a

library formed from the recombined polynucleotide sequences (see whole document, especially col. 4, lines 38-55).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 14 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stemmer (US 6,117,679 September 12, 2000) in view of Matsui et al (US 6,251,649 B1 June 26, 2001).

Stemmer teaches all of the limitations of claims 1-13, 15, 17-29 and 31-39 except this author does not explicitly teach Flap endonuclease. However, it was well known in the art at the time of the invention, as evidenced by Matsui et al., that Flap endonuclease has thermoresistance and high temperature activity properties and can be used in vitro recombination (see whole document, especially col. 2 line 40 to col. 3 line 9) and is useful in . Therefore, absent an unexpected result it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the teaching of Stemmer wherein a process of obtaining in vitro recombined polynucleotide sequences per se is utilized in combination with a Flap endonuclease having both thermoresistant and high temperature activity properties.

SUMMARY

13. No claims allowed.

CONCLUSION

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shar Hashemi whose telephone number is (703) 305-4840 and whose e-mail address is shar.hashemi@uspto.gov. However, the Office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner is on flex-time schedule and can be best reached on weekdays from 7:00 a.m. to 3:30 p.m. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119.

Any inquiry of a general nature, matching or filed papers or relating to the status of this application or proceeding should be directed to the Tracey Johnson for Art Unit 1637 whose telephone number is (703) 305-2982.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Center numbers for Group 1600 are Voice (703) 308-1235 and Before Final FAX (703) 872-9306 or After Final FAX (703) 308-9307.

GARY BENZION, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

January 3, 2002